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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/037,358	12/21/2001	Lawrence H. Lazarus	214777	7923

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/037,358	LAZARUS ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *2,4 and 9* is/are allowed.

6)☒ Claim(s) *1,3,5-8 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' election of Group I with traverse is acknowledged, as is the elected specie. Claims 5-8 and 10 are rejoined with the [redacted]elected group. Claims 1-10 are examined in this Office action.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-8 and 10 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In the specification, data is provided which shows that the claimed compounds can antagonize the *delta*-opioid receptor *in vitro*. The cited claims recite the term "treating" in the claimed method of use. The term "treating", in reference to a subject afflicted with a given disorder, is taken as an assertion that therapeutic efficacy can be achieved. As asserted in the specification the claimed compounds can be used to induce a state of analgesia in a mammal. Thus, claim 10 would encompass a method of inducing analgesia in a mammal that is suffering from pain. However, there is no evidence that the perception

of pain can be mitigated.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As for the "state of the art", there are examples of compounds which are effective to antagonize the *delta*-opioid receptor *in vitro*, and which also induce analgesia. However, it is not necessarily that case that if a compound can antagonize the *delta*-opioid receptor *in vitro*, that it will be effective to induce analgesia. First, the degree of antagonism may not be sufficient to achieve a perceptible effect, and second, the claimed compounds may be sufficiently vulnerable to metabolic enzymes that they will not survive long enough to reach the requisite receptor quickly enough to induce an analgesic effect. With respect to the matter of "unpredictability", the skilled pharmacologist would conclude that where receptor binding, receptor antagonism, and receptor activation are concerned, one cannot "predict" physiological or therapeutic efficacy on the basis of *in vitro* activity. Consider the following:

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, but discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.

- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]NH_2 (Et): effects on opioid receptor binding and activation" (*Journal of Peptide Research* (2000 Mar) 55 (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.

- Keith , "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.

- Xiao (*Biochemistry* **40**, 2860, 2001) has looked at the relationship between cAMP production in cells, and *in vivo* activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional determinantants of *in vivo* activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased *in vivo* insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an <u>increase</u> in *in vivo* insulinotropic activity. Thus, receptor activation is not necessarily predictive of *in vivo* activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) 2 (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [125I]-Nle4DPhe7-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity.

Thus, it is evident that whether one has demonstrated that a given compound is effective to

stimulate a receptor, or to antagonize a receptor, attempts to achieve a given physiological response using that compound lead to "unpredictable" results. Further, there are no "working examples" which demonstrate how to use the claimed compounds to induce analgesia. These facts, taken together with the nature of the invention, the state of the prior art, and the relative skill of those in that art, the skilled pharmacologist would conclude that "undue experimentation" would be required to practice the claimed invention.

✧

Claims 5-8 and 10 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "treating" implies an amelioration of the symptoms of a disease or disorder. The claims are indefinite as to what sorts of diseases and disorders might be encompassed, and indefinite also as to how one might recognize that the treatment had been successful. For example, suppose that the "disorder" is pain, and suppose also that as a consequence of administering the compound the delta-opioid receptor is antagonized, and the "mu" opioid receptor is agonized, but the patients' perception of pain is completely unaffected. Would applicants regard this as a successful treatment?

✧

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the

basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 3 are rejected under 35 U.S.C. §102(b) as being anticipated by Schiller (USP 5,773,881).

Schiller discloses (table I, col 7) the following peptide:

Dmt-Tic-Cha-Phe

Thus, the claims are anticipated.

✧

Claims 1 and 3 are rejected under 35 U.S.C. §102(b) as being anticipated by Schiller (USP

5,602,099).

Schiller discloses (col 7, line 25) the following peptide:

Dmt-Tic-Phe-Phe

Thus, the claims are anticipated.

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1 and 3 are rejected under 35 U.S.C. §103 as being unpatentable over Guerrini (*Bioorg Med Chem* **6**, 57-62, 1998).

Guerrini discloses (Table 1) the following peptide:

$[Dmt^1, Tic^2]$ DYN (1-11)NH_2

Guerrini does not disclose the sequence of Dynorphin A. However, as is known to the peptide chemist of ordinary skill, the first 5 (N-terminal) amino acids of Dynorphin A are the following:

Y-G-G-F-L

Thus, by replacing the N-terminal tyrosine with Dmt, and the penultimate residue with Tic, the resulting N-terminal sequence would be the following:

Dmt-Tic-Gly-Phe-Leu

This meets the requirement of claim 1 for "X" being an amino acid that is bonded to "Tic", and also meets the requirement for "Y" being a moiety that "comprises" an aromatic group.

Thus, the claims are rendered obvious.

✹

Reference "BD" was stricken from the IDS, because this reference may not have been obtained. An article by Lazarus with the following title was present in the parent application file, but the journal cannot be determined: "Size matters: New Frontiers in Designing potent *delta*-Opioid Antagonists", pages 24-29.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton

DAVID LUKTON
PATENT EXAMINER
GROUP 1653